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ORIGINAL PAPER

# A prospective study of dietary alpha-linolenic acid and the risk of prostate cancer (United States)

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**Abstract**
*Background* Alpha-linolenic acid (ALA) is the most common omega-3 fatty acid in the Western diet. The relation of dietary intake of ALA to prostate cancer risk remains unresolved.
*Objective* We prospectively evaluated total ALA and ALA from specific food sources including animal, fish, and plant sources in relation to prostate cancer risk.
*Design* A cohort of 29,592 male participants (age 55–74 years) in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was followed for an average of 5.1 years.
*Results* We ascertained 1,898 cases of total prostate cancer, of which 1,631 were organ-confined cases (stage T1b to T3a and N0M0) and 285 were advanced stage cases (stage ≥ T3b, N1, or M1). We found no association between total ALA intake and overall prostate cancer (multivariate *RR* comparing extreme quintiles = 0.94; 95% CI = 0.81–1.09; *P* for trend = 0.76). The corresponding *RR*s for organ-confined and advanced prostate cancer were 0.94 (95% CI = 0.80–1.10; *P* for trend = 0.80) and 0.83 (95% CI = 0.58–1.19; *P* for trend = 0.34), respectively. In addition, no relations were observed between ALA intake from any specific food source and the risks of total, organ-confined, or advanced prostate cancer. ALA intake also showed no association with low grade (Gleason sum < 7; 1,221 cases) tumors (*P* for trend = 0.23) or high grade (Gleason sum≥7; *n* = 677 cases) tumors (*P* for trend = 0.26).
*Conclusions* In this prospective study of predominantly Caucasian men who were screened annually for newly incident prostate cancer, dietary intake of total ALA and ALA from specific food sources was not associated with risk of total prostate cancer or prostate tumors that were defined by stage and grade.

**Keywords** Prostatic neoplasms · Alpha-linolenic acid · Epidemiology · Cohort studies

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## Introduction

Numerous [1–9], but not all [10–17] epidemiologic studies suggest that increased dietary intake of alpha-linolenic acid (ALA) enhances the risk of prostate cancer. One of the most recent studies on the topic [2] reported that the association between ALA intake and prostate cancer was

especially pronounced for mortality from prostate cancer, suggesting that ALA may stimulate progression from latent prostate cancer to invasive disease. This is disturbing given high prevalence of latent prostate cancer and increasing intake of ALA over time in the U.S. Availability of ALA as a proportion of total energy intake has increased 40% in recent decades in the U.S. [18]. ALA is the principal dietary omega-3 (n-3) fatty acid in U.S. diets, accounting for approximately 88% of total n-3 fatty acid intake [19].

The apparent adverse effects of increased ALA intake to prostate cancer risk that have been reported in previous epidemiologic studies may have been due to bias or chance. However, a positive association between ALA and prostate cancer has been observed in diverse populations, with available studies conducted in Uruguay [1], Spain [6], Norway [4], China [7], and the U.S. [2, 5, 8, 9]. Moreover, two individual investigations [1, 2] found a positive association for ALA both from animal and plant sources. Because men with high versus low intakes of ALA from animal sources show variation in potential confounding factors (such as increased smoking and lower levels of physical activity) that is distinct from men with high versus low intakes of ALA from plant sources, the positive findings between ALA from both animal and plant sources and prostate cancer that were seen in these two studies [1, 2] argue against major confounding. In addition, ALA does not represent a single dietary source which decreases the likelihood that positive findings seen in previous studies [1–9] were caused by chance.

The biological mechanisms through which ALA may increase prostate cancer risk are unknown, but ALA enhances peroxisomal $\beta$-oxidation [20], a process which generates hydrogen peroxide and may explain why ALA possesses greater potential for oxidative damage than eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in some studies [21]. Moreover, EPA and DHA have numerous anti-inflammatory properties that have been linked with decreased cancer risk [22], whereas ALA shows little influence on immune function and inflammatory cytokine production at feasible dietary levels [23].

Because the relation of dietary intake of ALA to prostate cancer risk remains unresolved [24, 25], we prospectively evaluated the association of total ALA and ALA from specific food sources with prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Our rationale for addressing different food sources of ALA was that animal products are both a source of ALA and are associated with increased prostate cancer risk [26], and it has been hypothesized [3] that positive associations between ALA and prostate cancer may be accounted for by intake of animal products or other unknown factors in animal fat.

## Methods

### Study population

The current study was conducted among male participants randomized to the screening arm of the PLCO Cancer Screening Trial, a multi-site clinical trial (Birmingham AL, Denver CO, Detroit MI, Honolulu HI, Marshfield WI, Minneapolis MN, Pittsburgh PA, Salt Lake City UT, St Louis MO, and Washington DC) in which participants were recruited from the general population, by direct mailings, advertisements, and other means. The objective of the parent study is to test the effectiveness of screening for these cancers and to identify early markers and etiologic determinants of cancer [27]. A total of 38,350 men between the ages of 55 and 74 years were enrolled into the screening arm between November 1993 and June 2001. As part of the trial, these men are screened annually for 5 years by prostate-specific antigen (PSA) test and annually for 3 years by digital rectal examination (DRE) and will be followed up for a minimum of 13 years from randomization for ascertainment of cancer outcomes. Study subjects provided written informed consent, and the study was approved by the institutional review boards of the U.S. National Cancer Institute and the ten screening centers. Details regarding the study have been described previously [27].

At randomization, study participants were requested to complete a self-administered baseline questionnaire that included items on socio-demographic factors, medical history, history of smoking and other health-related behaviors, and familial and personal history of cancer. In addition, all subjects randomized into the intervention arm completed a self-administered 137-item food frequency questionnaire (FFQ) that inquired about usual diet during the past year. Every year, study participants were requested to return a questionnaire that inquired about any cancer diagnosed by a health care provider, and if so, the type of cancer diagnosed.

For the current analysis, we excluded men who had a prior history of cancer other than non-melanoma skin cancer at baseline ($n$ = 791); men who did not undergo an initial screen ($n$ = 2,471); men who underwent an initial screen but for whom there was no subsequent contact ($n$ = 1,458); men who did not complete the baseline questionnaire ($n$ = 899); men who did not complete the dietary questionnaire ($n$ = 6,594); men who left more than seven items blank in the dietary questionnaire ($n$ = 253); men who reported energy intake in the top or bottom 1% of the reported energy intake distribution ($n$ = 634); and men for whom the initial screen occurred after 30 September 2002 ($n$ = 71). After exclusions, the population for analysis included 29,592 eligible men. The men in the final analysis were similar to the men excluded from the analytic cohort

with respect to age, level of education, smoking status, and family history of prostate cancer.

## Assessment of diet

We assessed usual dietary intake over the year prior to enrollment using a 137-item semi-quantitative FFQ (http://www3.cancer.gov/prevention/plco/DQX.pdf). Using a grid format, frequency of consumption was asked for 137 food items; in addition, usual portion size (small, medium, or large) was obtained for 77 items. Gram weights per portion size (small, medium, large) were assigned using data from the two 24-h recalls administered in the 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII) [28], a nationally representative survey conducted during the period when the FFQ was being used. In particular, the cut-points between small and medium, and between medium and large, correspond to the 25th and 75th percentiles for portion sizes reported by participants 51 years or older in the USDA 1994–1996 CSFII [28]. The choice of food items, the wording, and the assumptions for estimating nutrients and food groups for the PLCO FFQ incorporate elements of both cognitive [29, 30] and database [28] research.

We specifically queried about frequency of intake of fried fish (including on sandwiches), tuna, tuna salad, tuna casserole, shellfish (shrimp, crab, lobster, etc), and other fish (broiled or baked). The dietary questionnaire did not inquire specifically about the kind of fat usually used for frying, sautéing, or baking. Responses to the individual food items were converted to average daily intake of ALA from each food item. We combined the average daily intakes of ALA from individual food items to obtain composite ALA food groups. We considered total ALA, ALA from animal sources (red meat, poultry, fish, eggs, and dairy products), and ALA from plant sources (fruits, vegetables, grains, peanuts, and seed oils). We also considered separately ALA from animal sources excluding fish (red meat, poultry, eggs, and dairy products) and ALA from fish (fried fish, fish not fried, and shellfish).

## Case ascertainment

Men randomized to the screening arm of the PLCO trial underwent early detection for prostate cancer by serum PSA (at study entry and annually thereafter for 5 years) and DRE (at study entry and annually thereafter for 3 years). Men with a serum PSA value >4 ng/ml or a suspect DRE were referred to their medical care providers for further diagnostic evaluation. In addition, on each annual questionnaire participants were asked to report any diagnosis of prostate cancer during the prior year. For men with suspect prostate cancer by screening or men who reported prostate cancer on their annual questionnaire, medical records were abstracted to confirm the diagnosis and to obtain stage and grade information. Death certificates, autopsy data, and supporting medical/pathologic records were used to confirm the diagnosis and stage and grade information for participants who were deceased. The National Death Index was used to increase completeness of the data. Only confirmed cases were included in the analysis [31].

Dietary fats have been reported to be more strongly related to metastatic prostate cancers than localized prostate cancer in epidemiologic studies [3, 13, 32–34], suggesting that dietary fats may differentially influence advanced prostate cancer types versus indolent types [35]. Thus, we considered as separate prostate cancer endpoints cases that were regionally invasive or metastatic (≥ T3b, N1, or M1), and cases that were organ-confined or had minimal extraprostatic extension (T1b to T3a and N0M0). We also considered as separate endpoints cases with Gleason sum ≥ 7, and Gleason sum <7. Staging information was based on pathological stage if it was available. If pathological stage was not available, clinical stage was used. The Gleason score was based on the biopsy or prostatectomy Gleason, whichever value was higher.

## Data analysis

Person-time of follow-up for each participant was calculated from the time of randomization into the screening arm until the date of diagnosis, death, date of last questionnaire return, or the end of the study period (30 September 2002), whichever occurred first. Age-adjusted and multivariate relative risks were estimated using Cox proportional hazards regression [36] with age as the underlying time metric [37] using SAS V. 8.2 (SAS Institute, Cary, NC). We adjusted nutrient values for total energy intake using the residual method [38]. We included covariates that were associated with ALA and prostate cancer risk in our dataset and included covariates that have been reported to be potential confounders of prostate cancer relationships in the previous literature. The basic model included study center (nine indicator variables), race (White, Black, Asian/Pacific Islander, other), total number of screens (continuous), family history of prostate cancer (yes or no), history of diabetes (yes or no), smoking history (never, current, former, pipe/cigar only), body mass index (weight in kilograms divided by the height in meters squared) at baseline (quintiles), vigorous physical activity (0, 1, 2, 3, 4+ h/week), aspirin use (never use, <2 tablets/week, ≥ 2 tablets/week), vitamin E supplement use (0, 1–30, 31–400, >400 IU/day), intakes of total energy (quintiles), and

lycopene (quintiles). To distinguish between individual sources of ALA, we entered all measures of ALA from specific food sources into the model simultaneously. Additional control for red meat, processed meat, meat cooking methods, and meat-related heterocyclic amines did not alter the association of ALA to prostate cancer. Thus, these variables were not retained in our final models. Tests of linear trend across increasing quantiles of ALA intake were conducted by modeling the median values of quantiles of ALA as a single continuous variable in the models.

To examine whether the relation of ALA intake to prostate cancer risk varied between the first year (considered to include prevalent cases) and the remaining years of follow-up (considered to include incident cases), a time-dependent covariate (defined as the cross-product of follow-up time and ALA intake) was tested for statistical significance using the Wald test.

## Results

During the study period, we documented 1,898 new cases of prostate cancer. In our study population, ALA from animal sources contributed 42.5% of total ALA consumed while ALA from plant sources contributed 57.5% of total ALA intake. Mean intakes of ALA from individual food sources expressed as a percentage of total ALA intake were similar to U.S. consumption statistics [19]. ALA from specific food sources were not correlated with each other (Table 1). The largest individual food sources of ALA in the PLCO study population were regular salad dressings, mayonnaise, and milk.

To evaluate the potential for confounding by various study characteristics we investigated total ALA in relation to selected risk factors for prostate cancer (Table 2). Men in the highest quintile of ALA intake were more likely to report a personal history of diabetes and to consume more red meat and lycopene than men in the lowest quintile of ALA. In contrast, men with high ALA intakes were less likely to use supplemental vitamin E and aspirin than men with low ALA intakes.

We examined intakes of total ALA and ALA from individual food sources in relation to risk of total prostate cancer (Table 3). In age-adjusted and multivariate analyses, no association between total ALA and total prostate cancer was observed. The multivariate *RR* for men in the highest quintile of total ALA compared with those in the lowest quintile was 0.94 (95% CI = 0.81–1.09; *P* for trend = 0.76). No clear risk patterns emerged for any individual ALA food source with respect to total prostate cancer. Similar null associations were observed for ALA from individual food sources and organ-confined and advanced prostate cancer (data not shown).

To address the influence of intake of ALA on disease aggressiveness, we ran stratified analyses according to prostate tumor stage and grade (Table 4). The relations of ALA to both organ-confined and advanced stage disease were similar to the overall findings. Similarly, when we examined the association of ALA according to prostate tumor grade, ALA intake showed no association with tumors with a low Gleason sum (*P* for trend = 0.23) or tumors with a high Gleason sum (*P* for trend = 0.26).

We also examined the combination of ALA and linoleic acid (LA) in relation to risk of prostate cancer (Table 5). The relation of ALA to risk of prostate cancer did not differ by level of LA intake (*P* interaction=0.59). The association between ALA and prostate cancer also did not vary among subgroups of men defined by number of screening visits, family history of prostate cancer, history of diabetes, smoking history, body mass index, physical activity, aspirin use, vitamin E supplement use, intakes of total energy, long-chain n-3 fatty acids, and lycopene (all *P* for interaction>0.05). In addition, results did not differ between the first year of follow-up and the remaining observation period.

## Discussion

In this prospective study of predominantly Caucasian men who were screened annually for newly incident prostate cancer, we found that total ALA intake and ALA intake from individual food sources was not related to risk of prostate cancer. Our findings are largely compatible with those from two prospective studies [10, 11] and four case–control studies [12–15] that observed no association between dietary [12–14], serum [10, 11], adipose [15], or prostate tissue ALA levels [15] and prostate cancer risk. In contrast, three prospective [2–5] and five case–control

**Table 1** Mean intake and correlations of ALA from specific food sources in the screening arm of the PLCO Cancer Screening Trial at baseline

| Variable | ALA from animal sources (not including fish) | ALA from fish | ALA from plant sources |
|---|---|---|---|
| Mean intake (% of Total ALA) | 35.2 | 7.3 | 57.5 |
| Correlation | Pearson correlation coefficient | | |
| ALA from animal sources | 1.0 | – | – |
| ALA from fish | −0.05 | 1.0 | – |
| ALA from plant sources | 0.03 | −0.06 | 1.0 |

**Table 2** Selected characteristics of the 29,352 men in the screening arm of the PLCO Cancer Screening Trial by total ALA intake at baseline[a]

| Characteristic | Total ALA[b] | | | | | |
|---|---|---|---|---|---|---|
| | All | Q1 | Q2 | Q3 | Q4 | Q5 |
| Median ALA intake (g/day)[b] | 1.38 | 1.09 | 1.26 | 1.38 | 1.52 | 1.75 |
| Mean age at baseline (years) | 63.3 | 63.2 | 63.5 | 63.4 | 63.4 | 63.1 |
| Body mass index at baseline (kg/m$^2$) | 27.6 | 27.1 | 27.4 | 27.5 | 27.8 | 28.0 |
| Family history of prostate cancer (%) | 7.7 | 7.4 | 7.6 | 8.1 | 7.6 | 8.0 |
| History of diabetes (%) | 8.5 | 5.9 | 7.9 | 8.2 | 8.6 | 11.6 |
| Smoking | | | | | | |
| Current cigarettes (%) | 10.6 | 10.9 | 9.2 | 9.6 | 11.2 | 11.8 |
| Former cigarettes (%) | 52.0 | 54.4 | 53.3 | 52.0 | 50.3 | 50.3 |
| Ever pipe/cigars (%) | 7.9 | 8.2 | 7.9 | 7.9 | 8.1 | 7.5 |
| Mean daily intake | | | | | | |
| Energy (kcal/day) | 2,340 | 2,437 | 2,178 | 2,204 | 2,357 | 2,524 |
| Red meat (g/day)[b] | 93.6 | 79.2 | 89.9 | 97.1 | 100.8 | 100.5 |
| Long chain n-3 fatty acids (g/day)[b] | 0.15 | 0.11 | 0.14 | 0.14 | 0.16 | 0.18 |
| Linoleic acid (g/day)[b] | 13.4 | 10.7 | 12.1 | 13.1 | 14.1 | 16.3 |
| Lycopene ($\mu$g/day)[b] | 11,187 | 9579 | 10,890 | 11,421 | 11,692 | 11,944 |
| Supplemental vitamin E (IU/day) | 64.8 | 70.0 | 63.3 | 62.0 | 61.9 | 66.8 |
| Regular aspirin use (at least once daily; %) | 30.6 | 33.5 | 31.2 | 30.0 | 30.1 | 28.3 |
| Mean vigorous exercise (h/week) | 2.2 | 2.3 | 2.3 | 2.2 | 2.3 | 2.2 |
| Average number of screens (screens/year) | 0.82 | 0.81 | 0.81 | 0.83 | 0.82 | 0.81 |
| African-American (%) | 3.3 | 3.3 | 3.2 | 3.4 | 3.2 | 3.6 |
| Asian or Pacific Islander (%) | 4.0 | 3.6 | 3.6 | 3.5 | 3.7 | 5.5 |
| Other (Hispanic/Native American; %) | 1.9 | 1.9 | 2.0 | 1.8 | 2.2 | 1.8 |

[a]All values except age are standardized to the age distribution of the study population

[b]Nutrient values adjusted for total energy intake

studies [1, 6–9] reported a statistically significant [1–4, 6–8] or non-significant [5, 9] two- to four-fold increased risk of prostate cancer among men with high ALA exposure determined by dietary [1–3, 6] or blood [4, 5, 7–9] assessment.

Only two studies found a potential benefit of ALA on risk for prostate cancer. One prospective study from the Netherlands [16] noted a suggestion of an inverse association for intake of linolenic acid (relative risk comparing extreme quintiles = 0.76; 95% CI = 0.66–1.04; $P$ for trend = 0.09). A case–control study from the United States [17] examining non-cancerous prostatic tissue levels of fatty acids among men with localized prostate cancer found a statistically significant inverse association of prostatic ALA level with tumor invasiveness. However, little is known about whether prostatic ALA levels among prostate cancer cases reflect ALA exposure or could be affected by disease status [39].

When we examined the association between ALA and prostate cancer according to tumor grade, no associations were observed between ALA and well-differentiated (low grade) or undifferentiated (high grade) prostate tumors. Thus, our data do not support that ALA has potentially divergent effects according to prostate tumor grade, as is suggested by findings from an intervention study [40] using a flaxseed-supplemented low-fat diet among prostate cancer patients. That trial [40] reported a suggestive decrease in PSA among men with Gleason sums of 6 or less ($P$ = 0.10), whereas a suggestive increase in PSA ($P$ = 0.13) was observed among men with Gleason sums of 7 or more.

Apart from a true lack of an association, one possible reason for the null overall findings in our study is the methodological difficulty related to the measurement of dietary exposure to ALA. For example, current food composition databases are somewhat limited with respect to specific fatty acids such as ALA and may not always reflect the fatty acid composition of foods over time. In addition, our food-frequency questionnaire was not specifically designed to assess ALA intake. However, correlation coefficients relating ALA intake as assessed by a food-frequency questionnaire with serum ALA or adipose ALA have tended to be reasonable ($r$ = 0.28 and 0.42, respectively) [41]. Previous studies using serum, erythrocyte membranes, adipose, or prostate tissue as measures of exposure to ALA or exposure to other fatty acids also are prone to certain methodological constraints. For example, fatty acid levels in serum or erythrocyte membranes may not be superior to questionnaire-based assessments in representing long-term dietary fatty acid intake, although one study [39] showed a satisfactory correlation between erythrocyte membrane and adipose tissue n-3 fatty acid levels ($r$ = 0.41 for EPA; $r$ = 0.43 for DHA).

Our study has a number of strengths. It is one of the few prospective studies of ALA and the risk of prostate cancer

**Table 3** Relative risk of total prostate cancer in relation to intake of ALA in the screening arm of the PLCO Cancer Screening Trial

| Variable | Quintile | | | | | *P* (trend) |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Total ALA | | | | | | |
| Median adjusted intake (g/day)[a] | 1.09 | 1.26 | 1.38 | 1.52 | 1.75 | |
| Cases (*n*) | 396 | 362 | 388 | 390 | 362 | |
| Age-adjusted *RR* | 1.0 | 0.89 | 0.97 | 0.98 | 0.94 | 0.76 |
| Multivariate *RR*[b] | 1.0 | 0.89 | 0.96 | 0.97 | 0.94 | 0.76 |
| 95% CI | – | 0.77–1.03 | 0.83–1.11 | 0.84–1.11 | 0.81–1.09 | |
| ALA from animal sources | | | | | | |
| Median adjusted intake (g/day)[a] | 0.23 | 0.34 | 0.41 | 0.50 | 0.66 | |
| Cases (*n*) | 400 | 393 | 380 | 369 | 356 | |
| Age-adjusted *RR* | 1.0 | 1.01 | 1.02 | 1.01 | 1.04 | 0.62 |
| Multivariate *RR*[b] | 1.0 | 1.03 | 1.05 | 1.04 | 1.06 | 0.45 |
| 95%CI | – | 0.89–1.19 | 0.91–1.22 | 0.90–1.21 | 0.91–1.23 | |
| ALA from animal sources (not fish) | | | | | | |
| Median adjusted intake (g/day)[a] | 0.17 | 0.27 | 0.34 | 0.42 | 0.58 | |
| Cases (*n*) | 413 | 401 | 326 | 402 | 356 | |
| Age-adjusted *RR* | 1.0 | 0.99 | 0.84 | 1.06 | 0.99 | 0.73 |
| Multivariate *RR*[b] | 1.0 | 1.01 | 0.87 | 1.09 | 1.01 | 0.62 |
| 95%CI | – | 0.88–1.17 | 0.75–1.02 | 0.94–1.26 | 0.87–1.17 | |
| ALA from fish | | | | | | |
| Median adjusted intake (g/day)[a] | 0.01 | 0.04 | 0.05 | 0.08 | 0.15 | |
| Cases (*n*) | 359 | 382 | 399 | 401 | 357 | |
| Age-adjusted *RR* | 1.0 | 1.04 | 1.08 | 1.09 | 1.01 | 0.95 |
| Multivariate *RR*[b] | 1.0 | 1.07 | 1.10 | 1.11 | 1.03 | 0.91 |
| 95%CI | – | 0.92–1.24 | 0.94–1.28 | 0.95–1.29 | 0.89–1.20 | |
| ALA from plant sources | | | | | | |
| Median adjusted intake (g/day)[a] | 0.34 | 0.45 | 0.54 | 0.64 | 0.85 | |
| Cases (*n*) | 382 | 416 | 375 | 375 | 350 | |
| Age-adjusted *RR* | 1.0 | 1.08 | 0.99 | 1.00 | 0.95 | 0.25 |
| Multivariate *RR*[b] | 1.0 | 1.10 | 0.99 | 1.00 | 0.96 | 0.28 |
| 95%CI | – | 0.95–1.26 | 0.86–1.15 | 0.87–1.16 | 0.83–1.10 | |

[a]Nutrient values adjusted for average energy intake

[b]Multivariate model adjusted for age, current body mass index, family history of prostate cancer, history of diabetes, smoking history, intake of total energy, lycopene, supplemental vitamin E, aspirin use, physical activity, number of screens, study center, and race

[2–5, 10, 11, 16]. Because we controlled for various purported risk factors for prostate cancer, potential confounding by these factors was likely minimized. A particular advantage was our ability to account for PSA screening because all men in our study underwent a standardized screening procedure, consisting of one PSA test at baseline and one PSA test annually thereafter. In addition, prostate cancer cases were detected and staged using a standardized protocol, minimizing potential misclassification of organ-confined and advanced prostate cancer endpoints.

Evidence from animal and cell culture studies suggests that individual n-3 fatty acids, especially EPA and DHA, inhibit prostate carcinogenesis [42]. Possible mechanisms include a reduction in the synthesis of arachidonic acid (AA)-derived eicosanoids by reducing the availability of AA, by competing with LA for the enzymes required for eicosanoid formation, and by increasing the rate of eicosanoid catabolism [42]. However, little is known about the biological mechanisms through which ALA, the parent of all n-3 fatty acids, might relate to prostate cancer development. The sparse animal data available show that prostate tumor growth is not prevented in mice fed linseed oil (containing about 50% ALA) as compared with mice fed corn oil rich in LA [43]. Similarly, in rats the incidence of chemically induced prostate tumors is not reduced by feeding perilla oil (another linolenic acid-rich oil) as compared with rats fed corn oil [44].

The findings from these animal studies are difficult to interpret because the assigned diets produced no differences in the percentages of LA in the prostate tumor cell phospholipids between the mice fed linseed or perilla oil compared to those fed corn oil [43, 44]. Furthermore, these studies could have missed a potential adverse effect of ALA on prostate tumor growth because they compared the effects of ALA with those of LA, a putative prostate tumor promoter [45]. Intriguingly, one of these studies found that the perilla oil diet decreased the incidence of prostatic intraepithelial neoplasia (PIN) in the presence of testosterone [44], suggesting that ALA may specifically protect against the development of early-stage or androgen-sensitive prostate tumors. Paradoxically, mice fed linseed oil showed an increase in prostate tumor EPA levels but a decrease in DHA levels compared with those fed corn oil [43], suggesting that DHA biosynthesis may be down-regulated at high concentrations of ALA [46]. More research is needed

**Table 4** Multivariate relative risk of prostate cancer according to tumor stage and grade in relation to intake of total ALA in the screening arm of the PLCO Cancer Screening Trial[a]

| | Quintile | | | | | *P* (trend) |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Organ confined or minimal extraprostatic extension | | | | | | |
| Cases (*n*) | 333 | 311 | 327 | 341 | 301 | |
| Multivariate *RR* | 1.0 | 0.92 | 0.98 | 1.02 | 0.94 | 0.80 |
| 95% CI | | 0.79–1.07 | 0.84–1.14 | 0.87–1.19 | 0.80–1.10 | |
| | Tertile | | | | | |
| | 1 | | 2 | 3 | | |
| Regionally invasive or metastatic | | | | | | |
| Cases (*n*) | 97 | | 95 | 93 | | |
| Multivariate *RR* | 1.0 | | 1.28 | 0.83 | | 0.34 |
| 95% CI | | | 0.92–1.78 | 0.58–1.19 | | |
| | Quintile | | | | | |
| | 1 | 2 | 3 | 4 | 5 | |
| Gleason grade <7 | | | | | | |
| Cases (*n*) | 265 | 235 | 262 | 240 | 219 | |
| Multivariate *RR* | 1.0 | 0.88 | 0.99 | 0.91 | 0.88 | 0.23 |
| 95% CI | | 0.73–1.04 | 0.83–1.17 | 0.76–1.08 | 0.73–1.05 | |
| Gleason grade ≥7 | | | | | | |
| Cases (*n*) | 131 | 127 | 126 | 150 | 143 | |
| Multivariate *RR* | 1.0 | 1.02 | 0.86 | 0.93 | 0.89 | 0.26 |
| 95% CI | | 0.79–1.33 | 0.67–1.12 | 0.72–1.19 | 0.69–1.14 | |

[a]Multivariate model adjusted for age, current body mass index, family history of prostate cancer, history of diabetes, smoking history, intake of total energy, lycopene, supplemental vitamin E, aspirin use, physical activity, number of screens, study center, and race.

**Table 5** Multivariate relative risk of total prostate cancer in relation to the combination of intake of alpha-linolenic acid and linoleic acid in the screening arm of the PLCO Cancer Screening Trial[a]

| Tertile of linoleic acid | Quintile of ALA | | | | | *P* (trend) |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| 1 | | | | | | |
| Cases (*n*) | 307 | 213 | 119 | 41 | 11 | |
| Multivariate *RR* | 1.21 | 1.18 | 1.20 | 1.02 | 1.15 | |
| 95% CI | 0.85–1.72 | 0.82–1.69 | 0.82–1.76 | 0.65–1.62 | 0.58–2.28 | 0.31 |
| 2 | | | | | | |
| Cases (*n*) | 55 | 113 | 113 | 179 | 73 | |
| Multivariate *RR* | 1.06 | 0.97 | 1.10 | 1.09 | 1.02 | |
| 95% CI | 0.69–1.63 | 0.66–1.42 | 0.76–1.59 | 0.76–1.58 | 0.68–1.53 | 0.78 |
| 3 | | | | | | |
| Cases (*n*) | 34 | 36 | 36 | 170 | 278 | |
| Multivariate *RR* | 1.0 | 0.74 | 1.09 | 1.22 | 1.12 | 0.23 |
| 95% CI | – | 0.46–1.18 | 0.73–1.62 | 0.84–1.76 | 0.79–1.60 | |
| *P* (interaction) | | | | | | 0.59 |

[a]Multivariate model adjusted for age, current body mass index, family history of prostate cancer, history of diabetes, smoking history, intake of total energy, lycopene, supplemental vitamin E, aspirin use, physical activity, number of screens, study center, and race

to determine whether high versus low dietary availability of ALA differentially affects the terminal step beyond EPA synthesis of the DHA biosynthetic pathway.

In vitro data on ALA and prostate cancer are limited, and results vary. One study showed that ALA increased growth of the PC-3, LNCaP, and TSU cell lines [47]. In contrast, two studies using DU-145 cells found that ALA suppressed proliferation of DU-145 cells [48] and increased cell death at physiological ALA concentrations [49]. The former study also found that ALA inhibited the production of urokinase-type plasminogen activator [48], an important protease enzyme that is thought to enhance carcinogenesis. Another study using the DU-145 cell line showed that ALA decreased androgen receptor capacity and increased estrogen receptor capacity [50], suggesting that ALA modulates steroid hormone receptor binding. Taken together, previous experimental studies have yielded inconsistent findings which may be attributable to variation in cell culture growth conditions or differences in the concentrations of ALA and serum used in the cell culture medium.

In summary, we found no association between dietary intake of total ALA or ALA from specific food sources and risk of prostate cancer in this cohort of predominantly Caucasian men. We also did not observe any relation of ALA to risk of prostate tumors that were characterized by stage or grade.

## References


1. De Stefani E, Deneo-Pellegrini H, Boffetta P, Ronco A, Mendilaharsu M (2000) Alpha-linolenic acid and risk of prostate cancer: a case-control study in Uruguay. Cancer Epidemiol Biomarkers Prev 9:335–338
2. Leitzmann MF, Stampfer MJ, Michaud DS, Augustsson K, Colditz GC, Willett WC, Giovannucci EL (2004) Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr 80:204–216
3. Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC (1993) A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst 85:1571–1579
4. Harvei S, Bjerve KS, Tretli S, Jellum E, Robsahm TE, Vatten L (1997) Prediagnostic level of fatty acids in serum phospholipids: omega-3 and omega-6 fatty acids and the risk of prostate cancer. Int J Cancer 71:545–551
5. Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL, Stampfer MJ (1994) Prospective study of plasma fatty acids and risk of prostate cancer. J Natl Cancer Inst 86:281–286
6. Ramon JM, Bou R, Romea S, Alkiza ME, Jacas M, Ribes J, Oromi J (2000) Dietary fat intake and prostate cancer risk: a case-control study in Spain. Cancer Causes Control 11:679–685
7. Yang YJ, Lee SH, Hong SJ, Chung BC (1999) Comparison of fatty acid profiles in the serum of patients with prostate cancer and benign prostatic hyperplasia. Clin Biochem 32:405–409
8. Newcomer LM, King IB, Wicklund KG, Stanford JL (2001) The association of fatty acids with prostate cancer risk. Prostate 47:262–268
9. Godley PA, Campbell MK, Gallagher P, Martinson FE, Mohler JL, Sandler RS (1996) Biomarkers of essential fatty acid consumption and risk of prostatic carcinoma. Cancer Epidemiol Biomarkers Prev 5:889–895
10. Mannisto S, Pietinen P, Virtanen MJ, Salminen I, Albanes D, Giovannucci E, Virtamo J (2003) Fatty acids and risk of prostate cancer in a nested case-control study in male smokers. Cancer Epidemiol Biomarkers Prev 12: 1422–1428
11. Laaksonen DE, Laukkanen JA, Niskanen L, Nyyssonen K, Rissanen TH, Voutilainen S, Pukkala E, Hakkarainen A, Salonen JT (2004) Serum linoleic and total polyunsaturated fatty acids in relation to prostate and other cancers: a population-based cohort study. Int J Cancer 111:444–450
12. Andersson SO, Wolk A, Bergstrom R, Giovannucci E, Lindgren C, Baron J, Adami HO (1996) Energy, nutrient intake and prostate cancer risk: a population-based case-control study in Sweden. Int J Cancer 68:716–722
13. Bairati I, Meyer F, Fradet Y, Moore L (1998) Dietary fat and advanced prostate cancer. J Urol 159:1271–1275
14. Meyer F, Bairati I, Fradet Y, Moore L (1997) Dietary energy and nutrients in relation to preclinical prostate cancer. Nutr Cancer 29:120–126
15. Mamalakis G, Kafatos A, Kalogeropoulos N, Andrikopoulos N, Daskalopulos G, Kranidis A (2002) Prostate cancer vs hyperplasia: relationships with prostatic and adipose tissue fatty acid composition. Prostaglandins Leukot Essent Fatty Acids 66:467–477
16. Schuurman AG, van den Brandt PA, Dorant E, Brants HA, Goldbohm RA (1999) Association of energy and fat intake with prostate carcinoma risk: results from The Netherlands Cohort Study. Cancer 86:1019–1027
17. Freeman VL, Meydani M, Yong S, Pyle J, Flanigan RC, Waters WB, Wojcik EM (2000) Prostatic levels of fatty acids and the histopathology of localized prostate cancer. J Urol 164:2168–2172
18. Raper NR, Cronin FJ, Exler J (1992) Omega-3 fatty acid content of the US food supply. J Am Coll Nutr 11:304–308
19. Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, Hargrove RL, Zhao G, Etherton TD (2000) Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr 71:179S–188S
20. Sprecher H (1996) New advances in fatty-acid biosynthesis. Nutrition 12:S5–S7
21. Saito M, Kubo K (2003) Relationship between tissue lipid peroxidation and peroxidizability index after alpha-linolenic, eicosapentaenoic, or docosahexaenoic acid intake in rats. Br J Nutr 89:19–28
22. Healy DA, Wallace FA, Miles EA, Calder PC, Newsholm P (2000) Effect of low-to-moderate amounts of dietary fish oil on neutrophil lipid composition and function. Lipids 35:763–768
23. Calder PC (2001) Omega 3 polyunsaturated fatty acids, inflammation and immunity. World Rev Nutr Diet 88:109–116
24. Attar-Bashi NM, Frauman AG, Sinclair AJ (2004) Alpha-linolenic acid and the risk of prostate cancer. What is the evidence? J Urol 171:1402–1407
25. Brouwer IA, Katan MB, Zock PL (2004) Dietary alpha-linolenic acid is associated with reduced risk of fatal coronary heart disease, but increased prostate cancer risk: a meta-analysis. J Nutr 134:919–922
26. Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E (2001) A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes Control 12:557–567
27. Gohagan JK, Prorok PC, Hayes RB, Kramer BS (2000) The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials 21:251S–272S
28. Subar AF, Midthune D, Kulldorff M, Brown CC, Thompson FE, Kipnis V, Schatzkin A (2000) Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. Am J Epidemiol 152:279–286
29. Subar AF, Thompson FE, Smith AF, Jobe JB, Ziegler RG, Potischman N, Schatzkin A, Hartman A, Swanson C, Kruse L et al. (1995) Improving food frequency questionnaires: a qualitative approach using cognitive interviewing. J Am Diet Assoc 95:781–788, quiz 789–790
30. Thompson FE, Subar AF, Brown CC, Smith AF, Sharbaugh CO, Jobe JB, Mittl B, Gibson JT, Ziegler RG (2002) Cognitive research enhances accuracy of food frequency questionnaire reports: results of an experimental validation study. J Am Diet Assoc 102:212–225
31. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, Fogel R, Gelmann EP, Gilbert F, Hasson MA, Hayes RB, Johnson CC, Mandel JS, Oberman A, O'Brien B, Oken MM, Rafla S, Reding D, Rutt W, Weissfeld JL, Yokochi L, Gohagan JK (2000) Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 21:273S–309S
32. Whittemore AS, Kolonel LN, Wu AH, John EM, Gallagher RP, Howe GR, Burch JD, Hankin J, Dreon DM, West DW (1995) Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. J Natl Cancer Inst 87:652–661

33. Kristal AR, Cohen JH, Qu P, Stanford JL (2002) Associations of energy, fat, calcium, and vitamin D with prostate cancer risk. Cancer Epidemiol Biomarkers Prev 11:719–725
34. Terry P, Lichtenstein P, Feychting M, Ahlbom A, Wolk A (2001) Fatty fish consumption and risk of prostate cancer. Lancet 357:1764–1766
35. Dwyer JT (1997) Human studies on the effects of fatty acids on cancer: summary, gaps, and future research. Am J Clin Nutr 66:1581S–1586S
36. Cox DR (1972) Regression models and lifetables (with discussions) J R Stat Soc 34:187–220
37. Korn EL, Graubard BI, Midthune D (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol 145:72–80
38. Willett WC (1998) Nutritional epidemiology. Oxford University Press, New York, NY
39. Godley PA, Campbell MK, Miller C, Gallagher P, Martinson FE, Mohler JL, Sandler RS (1996) Correlation between biomarkers of omega-3 fatty acid consumption and questionnaire data in African American and Caucasian United States males with and without prostatic carcinoma. Cancer Epidemiol Biomarkers Prev 5:115–119
40. Demark-Wahnefried W, Price DT, Polascik TJ, Robertson CN, Anderson EE, Paulson DF, Walther PJ, Gannon M, Vollmer RT (2001) Pilot study of dietary fat restriction and flaxseed supplementation in men with prostate cancer before surgery: exploring the effects on hormonal levels, prostate-specific antigen, and histopathologic features. Urology 58:47–52
41. Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA (1999) Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 150:75–87
42. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A (2004) Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 79:935–945
43. Connolly JM, Coleman M, Rose DP (1997) Effects of dietary fatty acids on DU145 human prostate cancer cell growth in athymic nude mice. Nutr Cancer 29:114–119
44. Mori T, Imaida K, Tamano S, Sano M, Takahashi S, Asamoto M, Takeshita M, Ueda H, Shirai T (2001) Beef tallow, but not perilla or corn oil, promotion of rat prostate and intestinal carcinogenesis by 3,2'-dimethyl-4-aminobiphenyl. Jpn J Cancer Res 92:1026–1033
45. Rose DP (1997) Effects of dietary fatty acids on breast and prostate cancers: evidence from in vitro experiments and animal studies. Am J Clin Nutr 66:1513S–1522S
46. Langelier B, Furet JP, Perruchot MH, Alessandri JM (2003) Docosahexaenoic acid membrane content and mRNA expression of acyl-CoA oxidase and of peroxisome proliferator-activated receptor-delta are modulated in Y79 retinoblastoma cells differently by low and high doses of alpha-linolenic acid. J Neurosci Res 74:134–141
47. Pandalai PK, Pilat MJ, Yamazaki K, Naik H, Pienta KJ (1996) The effects of omega-3 and omega-6 fatty acids on in vitro prostate cancer growth Anticancer Res 16:815–820
48. du Toit PJ, van Aswegen CH, du Plessis DJ (1996) The effect of essential fatty acids on growth and urokinase-type plasminogen activator production in human prostate DU-145 cells. Prostaglandins Leukot Essent Fatty Acids 55:173–177
49. Motaung E, Prinsloo SE, van Aswegen CH, du Toit PJ, Becker PJ, du Plessis DJ (1999) Cytotoxicity of combined essential fatty acids on a human prostate cancer cell line. Prostaglandins Leukot Essent Fatty Acids 61:331–337
50. Prinsloo SE, van Aswegen CH (2002) Effect of fatty acids on estradiol and testosterone binding to whole DU-145 prostate cells Prostaglandins Leukot Essent Fatty Acids 66:419–425